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Clinical, morphological and immunohistochemical characterization of cutaneous lymphocytosis in 23 cats

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Abstract Clinical, morphological and immunohistochemical features of cutaneous lymphocytosis, an uncommon disease histologically resembling well-differentiated malignant lymphoma, were characterized in 23 cats. Clinical outcome was correlated with histomorphology and immunophenotype in an attempt to predict benign vs. malignant behaviour. The disease mainly affected older cats. Lesions were solitary in 61% of cats and often characterized by alopecia (73.9%), as well as erythema, scaling and ulceration. The lateral thorax was most commonly affected (43.5%). Pruritus was frequent (65.2%). Systemic signs included anorexia and weight loss. Morphologically, lesions were characterized by dermal infiltrations of well-differentiated $CD3^+$ T-cells (100%) and aggregates of $CD79^+$ B-cells (64.3%). Cutaneous lymphocytosis is slowly progressive and relatively benign, although in some cats systemic signs led to euthanasia. Four of 12 euthanized cats and one live cat also had lymphoid infiltrates in internal organs. Unfortunately, we were unable to predict clinical outcome by histological and immunohistochemical evaluations of skin lesions.

Keywords: alopecia, cat, cutaneous lymphocytosis, cutaneous lymphoma, lymphocytes, pseudolymphoma, T-cells.

INTRODUCTION

The term pseudolymphoma refers to a heterogeneous group of benign reactive T- or B-cell proliferations of well-differentiated lymphocytes in the skin of humans.[1] Lymphocytoma cutis and cutaneous lymphoid hyperplasia are other terms used to describe this disease in humans.[1,2] The concept of cutaneous B-cell pseudolymphoma was introduced in human medicine in 1923.[1] However, the concept of cutaneous T-cell pseudolymphoma has been widely accepted only since the early 1980s.[3] In pseudolymphoma of humans, an aberrant immune response to antigens may reflect a state of systemic immune dysregulation. Hypersensitivity reactions to various antigenic stimuli (including arthropod bites, viruses, contactants and drugs) were shown to be implicated causally.[1–7] As pseudolymphoma in humans can mimic both T- and B-cell lymphoma clinically and histologically, the distinction between these syndromes is important and problematic.[1,3–5]

The term pseudolymphoma implies a mimicry of neoplasia. In contrast, the term cutaneous lymphocytosis lacks specificity, as it implies neither a specific disease, nor a causation, but simply designates a process of accumulation of lymphocytes in the skin. Lymphoid infiltrates resembling pseudolymphoma of humans (cutaneous lymphocytosis) have been observed in dogs and cats.[8,9] To the authors' knowledge there are no recent reports of this entity in the veterinary literature. The purpose of this study was to characterize the clinical and morphological features of cutaneous lymphocytosis in 23 cats, with emphasis on clinical outcome of each case, in an attempt to identify potential differentiating and predictive features of benign vs. malignant behaviour. Long-term analysis of clinical outcome and prognosis are essential to a better understanding of these syndromes in order to accurately differentiate hyperplasia from neoplasia.

MATERIALS AND METHODS

Case material and histological examination

Twenty-three cats were selected for inclusion in this study based on skin biopsy samples submitted to one of the authors (TLG). Biopsy samples of lesional skin were submitted in 10% neutral buffered formalin. Fixed specimens were dehydrated in graded ethanol, cleared in xylene and embedded in paraffin. Paraffin sections (5 μm) were stained with haematoxylin and eosin (H&E) or used for immunohistochemical evaluation (see below).

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Morphological features were evaluated on H&E-stained sections. For the purpose of the study, feline cutaneous lymphocytosis was defined as an infiltration of the dermis by a monomorphous and dense population of well-differentiated lymphocytes.

Immunohistochemical evaluation

Immunophenotyping of each tissue section was performed using a limited panel of monoclonal antibodies specific for feline leukocyte antigens. These included the panleukocyte marker CD18 (clone Fe3.9F2; P. F. Moore, UC Davis, CA, USA), the T-cell marker CD3ε (Serotec Inc., Raleigh, NC, USA) and the B-cell marker CD79a (clone HM57; Dako Corp., Carpinteria, CA, USA).

Immunohistochemical staining was performed using a standard streptavidin-biotin technique as previously described[10] with the following modification for paraffin. Sections were deparaffinized in two 10-min changes of xylene followed by gradual rehydration through alcohol to phosphate buffered saline, pH 7.2. Tissue antigens were steam heat-retrieved in citrate buffer pH 6 (Dako Corp.) for 30 min followed by cooling for 20 min. The secondary biotinylated reagent for the mouse monoclonal antibodies, and the tertiary streptavidin reagent were obtained in predilute kit form (Biocare Medical, Walnut Creek, CA, USA) and applied for 10 min each at room temperature. A biotinylated goat antirat secondary reagent was used for the rat monclonal CD3ε. All the secondary antibodies were absorbed with 0.02% heat inactivated normal cat serum before use. Negative controls were prepared by omitting the primary antibody and substituting a mouse or rat myeloma IgG correlate.

Clinical data

Clinical data were obtained by mailing a questionnaire to the submitting clinicians. Desired information included signalment, age of onset, duration of disease, sites and characterization of cutaneous lesions, presence or absence of pruritus, evolution of skin lesions, involvement of sites other than skin, treatment and response to treatment, vaccination and drug history, and feline immunodeficiency virus (FIV) and feline leukaemia virus (FeLV) status. Additional information was obtained from all submitting clinicians via telephone interviews and included progression of the cutaneous lesions, response to therapy, development of systemic signs if any, life status and cause for euthanasia. Clinical outcome information was continuously pursued and recorded.

RESULTS

Animals and tissue samples

Tissue sections from 23 cats were compatible with cutaneous lymphocytosis. Five of 23 cats had skin biopsies performed on multiple occasions, yielding 28 different total tissue samples.

Clinical findings

Age, gender and breed data are shown in Table 1. The mean age of the cats at time of diagnosis was of 12.3 years (median: 13 years, range 6–15 years). Fourteen cats were spayed females (61%) and nine were castrated males (39%). The domestic short-haired cat (DSH) was the most represented breed (61%). The remaining cats were domestic medium-haired (DMH; 13%), mixed-Persian (4.3%), Siamese (4.3%), and Burmese (4.3%).

The duration of disease at the time of diagnosis was between 2 weeks and 48 months (mean: 5.9 months, median: 1.75 months, Table 1). Data were not available for one cat. The mean duration of disease from the time of diagnosis until the end of the study in the 11/23 cats that remained alive was 23.3 months (median: 22 months, range: 7–54 months). The 12 cats that were euthanized had a mean duration of disease from the time of diagnosis to time of euthanasia of 13.1 months (median: 11 months, range: 1–49 months).

Skin lesions were variable (Table 2). Sixty-one per cent of cats presented with solitary lesions. The most frequent lesions were alopecia (73.9%), erythema, and scaling with or without crusting (Figs 1 and 2). Less commonly, alopecia and scaling were noted without erythema. Other less frequently reported lesions included alopecic erythematous plaques (30.4%; Figs 3 and 4), single or multiple nodular lesions (13%), solitary ulcers (4.35%) and miliary papules (4.35%). Ulceration or excoriation were common (47.8%). Proliferation of the foot pads and ulceration of the planum nasale were reported in 8.7% and 4.35% of the cats, respectively. Pruritus was reported in 15/23 cats (65.2%). Size of lesions was available in 14 cats and ranged from 1.5 cm in diameter to 10 by 12 cm (Table 2). Sites of lesions are shown in Table 2. The most frequently affected site was the thorax (43.5%). Other affected sites included legs (17.4%), pinnae (17.4%), flank (13%), neck (13%), abdomen (8.7%), foot pads (8.7%), between the scapulae (4.35%), elbow (4.35%), caudal thigh (4.35%), hip (4.35%), digit (4.35%) and planum nasale (4.35%).

Chemistry panels were performed in 10/23 cats (43.5%) and were within normal limits in nine cats. Liver enzymes were elevated in 1/10 cat (cat 5, exact values not available). Complete blood count (CBC), performed in 12/24 cats, revealed abnormal values in three cats: cat 3 had mild eosinophilia (exact value not available); cat 7 had leukocytosis (34 500; normal values: 5500–19 500) with neutrophilia (17 040; normal values: 2500–12 500) and lymphocytosis (10 695; normal values: 1500–7000) and cat 16 had leukocytosis (23 300) with lymphocytosis (11 883). FeLV and FIV results were negative in all 14 cats tested.

Histological findings

Microscopic examination of the 28 H&E-stained tissue sections revealed a moderate to marked perivascular to diffuse, superficial and deep dermal round cell infiltrate consistent with lymphocytes (Figs 5–7). Lymphocytes

Table 1. Signalment, age of onset, duration of disease and treatment in 23 cats with cutaneous lymphocytosis

Cat number	Sex	Breed	Age at time of diagnosis (years)	Duration of disease before diagnosis (months)	Duration of disease since diagnosis (months)	Total duration of disease (months)	Treatment/response	Comments
1	Fs	DSH	14	1.5	7	8.5	Oral dexamethasone/++	
2	Fs	DSH	14	48	11	59	Oral prednisolone Injectable/+ methylprednisolone acetate/0	
3	Fs	DSH	15	3	11	14	Topical triamcinolone/0 Oral dexamethasone/++	
4*	Fs	DSH	9	*Chronic*	12	Unknown	Injectable methylprednisolone acetate/0	
5*	Fs	DSH	13	1	11	12	Injectable methylprednisolone acetate/0 Oral prednisolone/0 Topical triamcinolone/0	
6*	Mc	DMH	10	1	7	8	Oral prednisolone/+	
7*	Fs	DMH	13	1	11	12	Injectable methylprednisolone acetate/+++	
8	Mc	DLH	15	29	16	45	Oral prednisolone/0 Injectable methylprednisolone acetate/+	
9*	Fs	DLH	13	5	5	10	Amitriptyline/0	
10*	Mc	DSH	14	4	7	11	Injectable methylprednisolone acetate/+	
11	Fs	DSH	15	1	54	55	Surgery/+++	
12*	Mc	DSH	11	2	10	12	Injectable methylprednisolone acetate/+++	Recurrence after 6 weeks
13	Fs	Persian mix	11	5	22	27	Oral prednisolone/0 Injectable methylprednisolone acetate/+++	Recurrence after 8 weeks
14	Fs	DSH	13	12	26	38	Topical betamethasone/+	
15*	Mc	DSH	10	3	12	15	Oral prednisolone/0 Surgery/0	
16*	Mc	DSH	13	1	13	14	Injectable triamcinolone/+ Oral prednisolone and chlorambucil/+++	
17	Fs	DSH	13	1	31	32	Oral dexamethasone/++	
18*	Mc	Siamese	6	5	1	6	Injectable triamcinolone/+ Oral dexamethasone/0 Oral dexamethasone and chlorambucil/0	
19*	Fs	DLH	12	1	19	20	Oral prednisolone/0 Oral prednisolone and lomustin/+++	
20	Fs	DSH	11	0.5	37	37.5	Oral prednisolone and chlorambucil/++	
21*	Mc	Burmese	12	1	49	50	Oral prednisolone/+	
22	Fs	DMH	12	2	19	21	None	Spontaneous resolution
23	Mc	DSH	14	1	22	23	Oral prednisolone and chlorambucil/+++	Initial spontaneous resolution followed by recurrence

*Cats that were euthanized. Fs, female spayed; Mc, male castrated; DSH, domestic short-haired cat; DMH, domestic medium-haired cat; DLH, domestic long-haired cat.
Response of cutaneous lesions to treatment: +++, complete resolution; ++, partial resolution; +, stabilization; 0, no response.

were characterized by small dark nuclei with compact chromatin, and a small (4/28, 14.3%) or moderate (15/28, 53.6%, Fig. 7) amount of pale amphophilic cytoplasm. The remaining nine sections (32.1%) were composed of both types of lymphocytes in approximately the same proportion. Mitotic figures were not observed. Eighteen of the 28 sections (64.3%) contained nodular aggregates of tightly packed lymphocytes with small nuclei and scant cytoplasm embedded in the diffuse more loosely arrange lymphoid population (Figs 5 and 6). These cells were smaller and had dense basophilic nuclei and scant cytoplasm. Mild epitheliotropism of both the epidermis and hair follicles was noted in 13/28 sections (46.4%) (Fig. 8). Histiocytes, mast cells, eosinophils and neutrophils were admixed in minimal to mild numbers in some cats. Moderate epidermal hyperplasia, excoriation and ulceration were noted occasionally.

Table 2. Clinical findings in 23 cats with cutaneous lymphocytosis

Cat number	Solitary/multiple	Site of lesions	Type of lesions	Size of lesions
1	M	Dorsal and lateral thorax	Plaques, erythema, alopecia, depigmentation, ulceration, crusting	5 × 6 cm to 8 × 10 cm
		Ventral chest	Alopecia, erythema	4 × 8 cm
		Footpads	Hyperplasia	
2	M	Left lateral thorax	Plaque, erythema, alopecia, scaling, crusting	4 × 5 cm
		Ears	Alopecia, erythema, scaling, crusting	Unknown
3	S	Left lateral thorax	Alopecia, erythema, scaling, excoriations	Unknown
4*	S	Neck	Alopecia, erythema, crusting.	Unknown
5*	S	Left abdomen	Plaque, erythema, alopecia, ulceration	3 cm
6*	S	Right thorax	Ulceration	Unknown
7*	M	Ventral thorax and digits	Plaques, erythema, alopecia, scaling, ulceration	Unknown
8	S	Left lateral thorax	Plaque, erythema, alopecia, scaling	6 × 5 cm
9*	M	Right elbow	Soft thick nodule, alopecia, erythema, depigmentation	Unknown
		Hip and legs	Alopecia, erythema, scaling, crusting, ulceration	6 × 8 cm
		Footpads	Hyperplasia	
10*	S	Dorsal lumbar	Alopecia, erythema, excoriations	Unknown
11	S	Left lateral caudal flank	Alopecia, erythema, scaling, ulceration	10 × 12 cm
12*	M	Dorsum, right metacarpus, pinnae	Alopecia, erythema, ulceration	1.5 cm
13	S	Left caudal thigh	Alopecia, erythema, ulceration	5 × 6 cm
14	S	Left flank	Alopecia, scaling	4 × 5 cm
15*	S	Left caudal flank	Alopecia, erythema, scaling	4 × 6 cm
16*	S	Between shoulders blades	Plaque, erythema	Unknown
17	M	Ear pinnae	Alopecia, erythema, scaling, crusting	Unknown
		Dorsal neck	Nodules	2–3 mm
		Planum nasale	Erythema, ulceration	Unknown
18*	M	Pinnae, neck	Alopecia, erythema, depigmentation, crusting, nodules	Unknown
		Thorax, legs	Alopecia, erythema, crusting	Unknown
19*	M	Abdomen	Alopecia, erythema, ulceration	Unknown
20	S	Right front leg	Plaque, erythema, alopecia, scaling	4 × 6 cm
21*	S	Right lateral caudal thorax	Alopecia, erythema, scaling	10/10 cm
22	S	Right cranio-lateral thorax	Alopecia, scaling	6 × 6 cm
23	M	Left and right lateral thorax	Alopecia, scaling	1 × 2 cm to 3 × 4 cm
		Base of ear pinnae	Miliary papules	1 mm

*Cats that were euthanized. S, solitary; M, multiple.

Immunohistochemistry findings

All infiltrates were strongly positive for the common leukocyte antigen CD18. The perivascular and diffuse dermal and intraepithelial infiltrate was composed of $CD3\varepsilon^+$ T-cells (Fig. 9). The small aggregates consisted of $CD79a^+$ B-cells (Fig. 10). Sparse, dispersed cells expressing CD79a were present also in 22 tissue sections (22/28, 78.6%). There were variable numbers of admixed $CD18^+$, $CD3^-$, $CD79a^-$ histiocytic cells.

Clinical outcome

Clinical outcome was available for all 23 cats. Details on the onset and the progression of the skin lesions were available in 17/23 cats (73.9%). Onset was acute, and progression was slow in all 17 cats. The lesions were reported to wax and wane in 10/17 cats. Eighteen of the 23 cats (78.3%) still had lesions at the end of the study, or at euthanasia. Spontaneous resolution of the lesions was noted in cats 22 and 23 (8.7%). Recurrence was seen after approximately 6–8 weeks in cat 23, while cat 22 has remained free of lesions for 18 months. Cats 2 and 23 had been given methimazole daily for treatment of previously diagnosed hyperthyroidism prior to the onset of cutaneous lymphocytosis. Complete resolution of the lesions after discontinuation of the methimazole was seen in cat 23, but lesions reoccurred after several weeks. For cats 19 and 23, hypersensitivity to food was considered initially. An elimination diet may have resulted in subtle improvement of the skin lesions initially, but was followed by recrudescence.

Therapy was performed in 22/23 cats (Table 1). Eleven cats received antibiotics, including cefadroxyl, amoxicillin, amoxicillin/acid clavulanate, clindamycin, ormetoprim/sulfadimethoxine and enrofloxacin, with no improvement. Surgical excision of solitary lesions was performed in 2/22 cats (9.1%) and was successful in one (cat 11) (Table 1). However, the lesion recurred 18 months after the first surgical excision and required a second intervention. Eighteen of the 22 cats (81.8%) were treated with glucocorticoids topically (triamcinolone, betamethasone) or orally (prednisolone or dexamethasone), or with injectable glucocorticoids (triamcinolone or methylprednisolone acetate), with variable response (Table 1). Six of the 18 cats showed a complete or a good initial resolution, while eight cats had only a moderate response (stabilization of the skin lesions), and four cats showed no response to any of the glucocorticoids that were used. Glucocorticoids, in conjunction with either chlorambucil or lomustine, were administrated orally to 5/22 cats (22.7%) with complete response in three cats, good response in one cat and no response in one cat (Table 1).

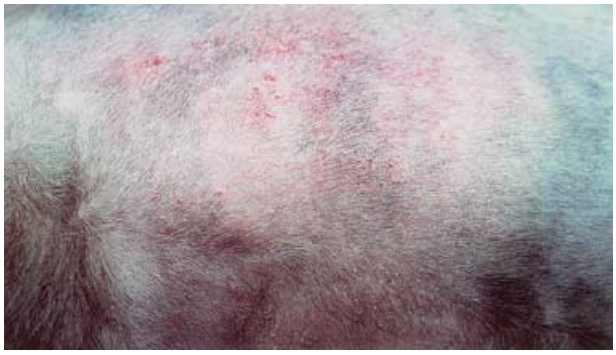

Figure 1. Lateral thorax; feline cutaneous lymphocytosis, cat 3. Alopecia, erythema, scaling and excoriation (courtesy of Dr H. T. Power).

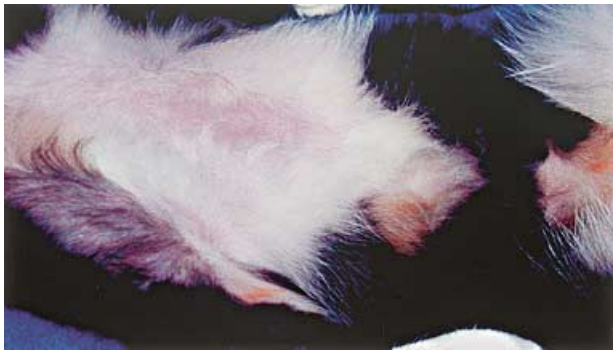

Figure 2. Ventral chest; feline cutaneous lymphocytosis, cat 1. Alopecia and erythema (courtesy of Dr S. Radowicz).

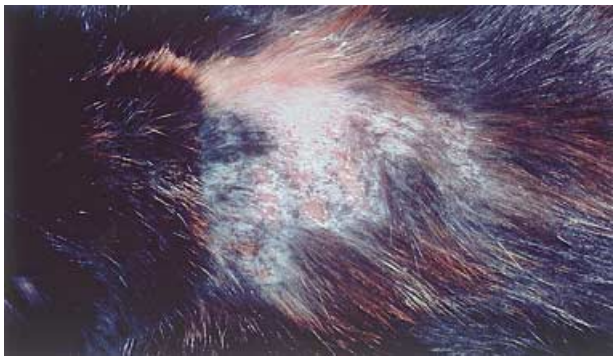

Figure 3. Dorsal thorax; feline cutaneous lymphocytosis, cat 1. Alopecic plaques with erythema, depigmentation, crusts and ulceration (courtesy of Dr S. Radowicz).

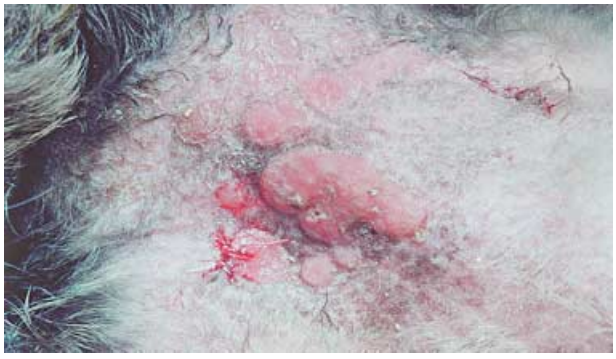

Figure 4. Ventral thorax; feline cutaneous lymphocytosis, cat 7. Alopecic plaques with erythema, scaling and ulceration. Note the resemblance with eosinophilic plaques (courtesy of Dr E. K. Smith).

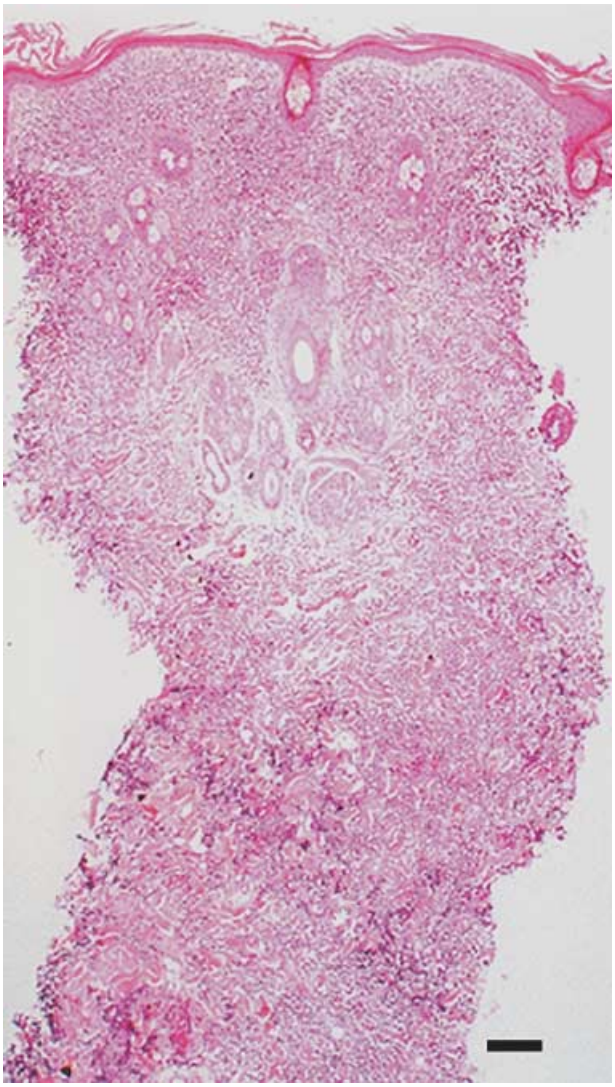

Figure 5. Skin; feline cutaneous lymphocytosis, cat 9. Superficial and deep lymphocytic dermal infiltrate (H&E, bar = 180 μm).

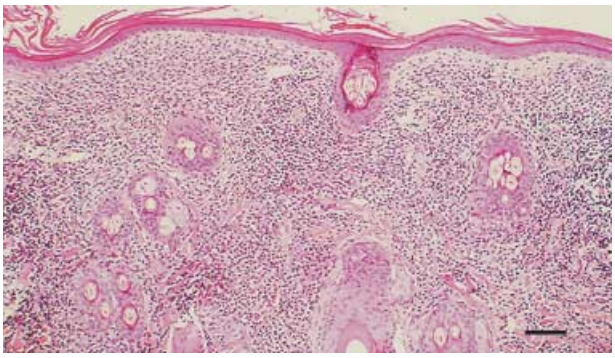

Figure 6. Skin; feline cutaneous lymphocytosis, cat 9. Marked diffuse lymphocytosis (H&E, bar = 70 μm).

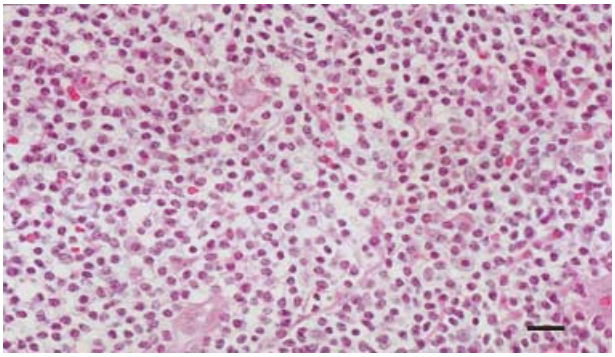

Figure 7. Skin; feline cutaneous lymphocytosis, cat 10. Well-differentiated lymphocytes compose the dermal infiltrate. Note cells with moderate pale cytoplasm (H&E, bar = 18 μm).

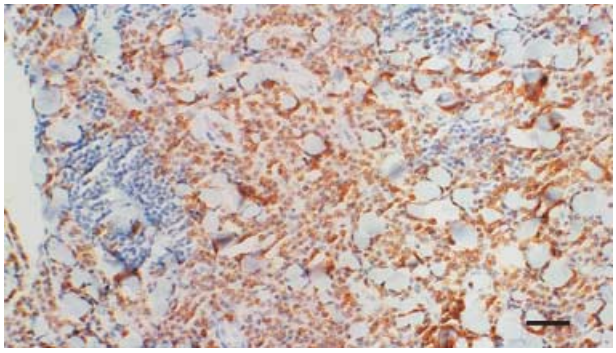

Figure 9. Skin; feline cutaneous lymphocytosis, cat 9. The dermal infiltrate is composed of CD3ε^{+} T-cells. Note the aggregates of negative stained B-cells. Immunostaining using CD3ε monoclonal antibody. Bar = 26 μm.

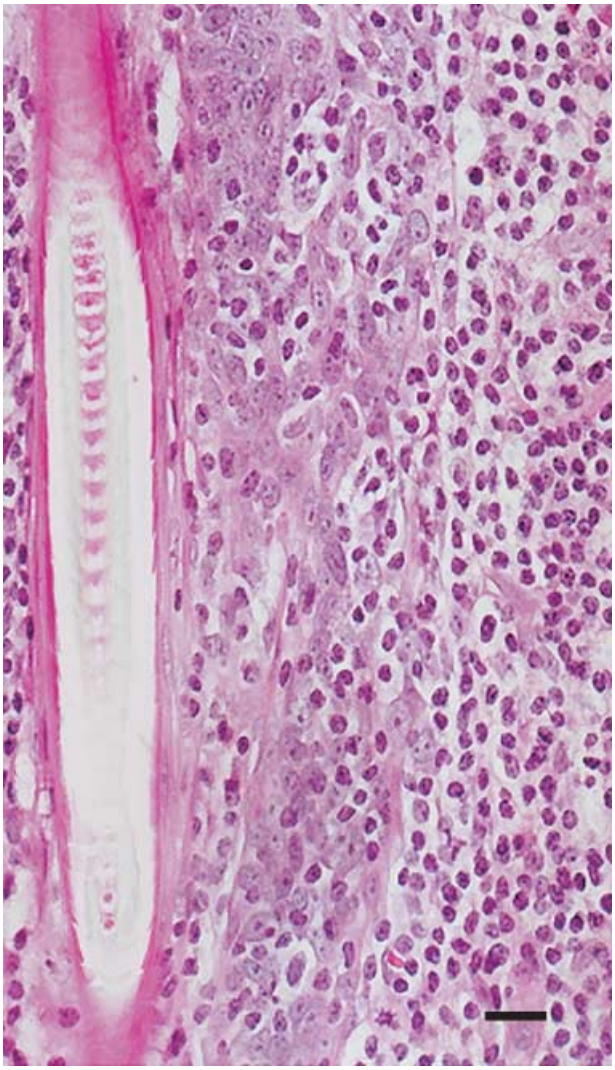

Figure 8. Skin; feline cutaneous lymphocytosis, cat 10. Epitheliotropism of the hair follicle. Note the slight infiltration of well-differentiated lymphocytes (H&E, bar = 18 μm).

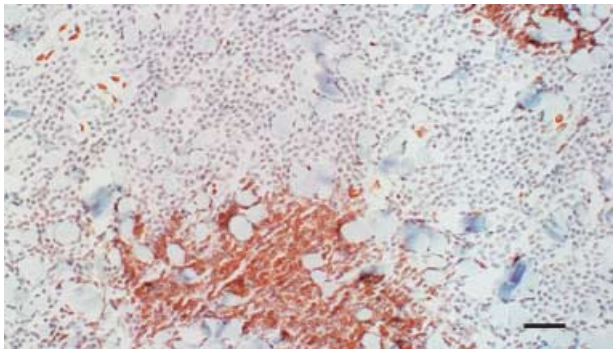

Figure 10. Skin; feline cutaneous lymphocytosis, cat 9. The aggregates are composed of CD79a^{+} B-cells. Note the weak false positive nuclear staining of the diffuse T-cell infiltrate. Immunostaining using CD79a monoclonal antibody. Bar = 37 μm.

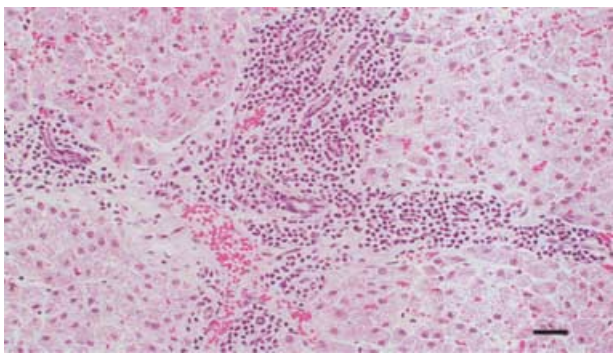

Figure 11. Liver; feline cutaneous lymphocytosis, cat 9. Note heavy portal infiltration of well-differentiated lymphocytes (H&E, bar = 37 μm).

The majority of the cats lived a long period of time with or without signs of systemic disease (Tables 1 and 3). By study completion, 12/23 cats (52%) were euthanized 1–49 months after diagnosis (mean: 13.1 months, median: 11 months). Causes for euthanasia are shown in Table 3. Six of the 12 cats showed decreased appetite and weight loss, indicating potential internal disease. In two cats the cause of euthanasia was unknown. The other four cats had pulmonary oedema, diabetes mellitus, squamous cell carcinoma and kidney failure, respectively. Necropsy was performed in 4/6 cats that had decreased appetite and weight loss, and revealed gross internal lesions in all four cats (Table 3). Cytological or histological examination of visceral organs was

Table 3. Causes of euthanasia in 12 cats with cutaneous lymphocytosis

Cat number	Cause of euthanasia/clinical findings	Gross findings/necropsy	Histological findings
4	Pulmonary oedema	Necropsy not performed	Not performed
5	Decreased appetite, weight loss. Ascites (milky appearance)	Necropsy not performed	Not performed
6	Cause unknown	Necropsy not performed	Not performed
7	Diabetes mellitus following methylprednisolone acetate injection	Necropsy not performed	Not performed
9	Decreased appetite, weight loss	Nodules on liver and pancreas, irregular kidneys	Infiltration of liver (Fig. 11), pancreas and kidney by T-cells
10	Decreased appetite, weight loss	Cytology of thoracic effusion and of masses on liver and spleen. Necropsy not performed	Infiltration by well-differentiated lymphocytes (immunohistochemistry not performed)
12	Cause unknown. Peripheral lymphadenopathy	Necropsy not performed	Not performed
15	Squamous cell carcinoma on the tongue	Necropsy not performed	Not performed
16	Decreased appetite, weight loss. Peripheral lymphadenopathy	Enlarged mesenteric lymph nodes, nodules on pancreas	Not performed
18	Decreased appetite, weight loss	Nodules on liver and pancreas, cardiomegaly	Infiltration of liver, pancreas, stomach and heart by well differentiated T-cells
19	Decreased appetite, weight loss, diarrhoea	Thickening of small intestine	Infiltration of small intestine by B cells, few T-cells
21	Kidney failure	Necropsy not performed	Not performed

performed in four euthanized cats (3/4 cats that were necropsied and one cat that was not necropsied but had fine needle aspirations performed when he was still alive) and showed monomorphic infiltrate of lymphocytes with morphological characteristics similar to those in the skin in all four cats (Table 3). Immunochemistry performed in 3/4 cats that were necropsied revealed that the lymphoid infiltrate was composed of $CD3\varepsilon^+$ T-cells in two of the three cats, and of $CD79a^+$ B-cells in one cat (Table 3). Only one of the 11 living cats (cat 23) showed systemic signs (decreased appetite and weight loss). Duodenal biopsy performed in that cat revealed a mucosal and submucosal infiltration by well-differentiated $CD3\varepsilon^+$ T-cells.

DISCUSSION

Feline cutaneous lymphocytosis is a relatively uncommon disease. In this study, the disease mainly affected older cats (mean and median age were 12.2 years and 13 years, respectively) and females were over represented. Breed predilections were not noted; 61% of the affected cats were DSH, which approximately reflects the cat population in the USA.

Although lesions varied, 73.9% of the cats had alopecia with or without erythema, and scaling and ulceration or excoriation, and 30% had erythematous plaques with or without ulceration. These cats had clinical features similar to some reported cases of cutaneous epitheliotropic lymphoma.[11,12] Nodular lesions were noted in only 13% of the cats and were always present with other lesions. Sixty-one per cent of the cats were presented for a solitary lesion. Pruritus was reported in 65.2% of the cats, presumably leading to the excoriation noted in some cases.

The classification of pseudolymphoma in humans is predominantly based on the type of lymphocytes that compose the infiltrate, the morphological appearance of the infiltrate and the distribution of the infiltrate with regard to the dermis and epidermis.[3,5] The infiltrate in humans in cutaneous pseudolymphoma is predominantly composed of well-differentiated small lymphocytes with a scant amount of cytoplasm, and can be either T- or B-cells.[3,5] The lymphoid infiltrates can be arranged in a superficial band, or form dermal nodules.[3,5] Although T-cell pseudolymphoma can be composed of a nodular infiltrate, they are often composed of a superficial band-like infiltrate.[3,5] Epitheliotropism can be present in T-cell pseudolymphoma, but it tends to be less severe than that seen in cutaneous epitheliotropic lymphoma.[3,5] Moreover, although less commonly, intraepidermal aggregates of lymphocytes referred to as Pautrier's aggregates can also be present in T-cell pseudolymphoma.[3,5] These features indicate that in humans the histological differentiation of T-cell pseudolymphoma and early stages of well-differentiated cutaneous lymphoma (epitheliotropic and nonepitheliotropic T-cell lymphoma) is often not possible.[3,5]

The classification system used for pseudolymphoma in humans cannot be entirely used in cats as the lesions differ from their human counterparts. All infiltrates seen in the 23 cats were composed of T-cells. B-cell lymphocytosis was not observed, as seen in humans. In cats, B cells were only encountered as small aggregates within the diffuse T cell proliferation in 64.3% of the samples. The morphology of the lymphoid infiltrate in cats varied between cases and included lymphocytes with slightly enlarged nuclei and moderate cytoplasm, as well as smaller lymphocytes with scant cytoplasm. Epitheliotropism was present in almost half of the samples of feline cutaneous lymphocytosis but was too mild to suggest epitheliotropic malignant lymphoma. Aggregates similar to Pautrier's aggregates were noted in one cat. As in humans, feline cutaneous lymphocytosis may be difficult to separate from early

well-differentiated (small cell) cutaneous malignant lymphoma.

Most cats with cutaneous lymphocytosis had protracted disease. Skin lesions were slowly progressive. Spontaneous resolution with no recurrence was seen in one cat. Therefore, cutaneous lymphocytosis appears to be a relatively benign or at least protracted disease in cats, as is pseudolymphoma in humans.

Some cats with cutaneous lymphocytosis had decreased appetite and weight loss, indicating potential internal disease, and were euthanized (Table 3). Some of these cats were shown to have visceral lymphoid infiltration. When performed, histological or cytological examination of internal organs or effusions revealed well-differentiated T-cell infiltrates in all but one cat. Interestingly, this cat with only a mild B-cell infiltration of the small intestine, with dispersed T-cells, had received an oral dose of lomustine 6 days prior to euthanasia, which may explain the absence of T-cell infiltration (Table 3).

For the five cats with confirmed systemic infiltration, it is not known if the lymphocytic infiltrates were first present in the skin or in internal organs, or if the infiltrate arose in both locations simultaneously. It is possible that there is a relationship between cutaneous lymphocytosis and systemic involvement. A strong correlation between lymphocytic cholangiohepatitis, inflammatory bowel disease and pancreatitis was shown in cats in a previous study.[13] In such cases, cutaneous lymphocytosis may represent a marker for internal lymphocytic infiltration.

In humans, the confusion of nosology of pseudolymphoma (cutaneous lymphocytosis) and its relationship to other lymphoproliferative disorders arises because of the observation that some patients with cutaneous pseudolymphoma eventually progress to develop malignant lymphoma.[5] Similarly, feline cutaneous lymphocytosis with systemic involvement might represent true malignant transformation of cutaneous lymphocytosis into lymphoma, or alternatively might represent early well-differentiated cutaneous lymphoma inappropriately diagnosed as lymphocytosis. It is possible that systemic lymphoid involvement may have been present in other cats that were euthanized due to systemic signs but did not have necropsy performed. Findings compatible with systemic lymphoid involvement, including ascites of milky appearance and enlarged mesenteric lymph nodes, were reported in two cats that had neither necropsy nor histological examination (Table 3).

The aetiology and pathogenesis of pseudolymphoma in humans is largely unknown.[1,3,4] Processes such as lymphomatoid drug eruptions, lymphomatoid contact dermatitis, persistent nodular arthropod-bite reactions, nodular scabies, actinic reticuloid, and lymphomatoid papulosis have been associated.[5] Hence, it is believed that benign hyperplastic lymphoid infiltrates may represent an exaggerated immune reaction to diverse external antigens including drugs, insect bites, scabies, injection of arthropod venom, vaccination, allergen-specific immunotherapy, contactants, trauma, acupuncture, tattoo dyes and gold pierced ear-rings.[1–7]

It is likely that feline cutaneous lymphocytosis could also be the result of a persistent antigenic stimulus, as suspected in humans. The improvement or the resolution of the skin lesions reported in some cats with the administration of glucocorticoids or other immunosuppressive therapy favours such a hypothesis. Vaccination was reported to trigger the disease in humans.[6] The lateral thorax, shoulder, dorsal neck, flank and rear legs are common vaccine sites in cats. Many of the lesions in our study were found in these locations, suggesting possible causation. Recently, early lymphocytic infiltration of the skin resembling cutaneous lymphocytosis was found by the authors overlying a typical vaccine site sarcoma in a cat (T. L. Gross, IDEXX Veterinary Services and California Dermatopathology Service; 2003, unpublished data). Some drugs are well known to induce cutaneous pseudolymphoma in humans.[1,3–5] One cat showed initial complete resolution of the lesions after discontinuation of methimazole, but lesions recurred after several weeks. The drug history was incomplete in some cats, and therefore the possibility of some lesions being drug-induced cannot be excluded. An elimination diet performed in two cats resulted in subtle improvement of the skin lesions initially, but was followed by recrudescence. Temporary improvement reported in these cats may simply reflect the waxing and waning nature of this disease.

Cutaneous epitheliotropic lymphoma-like cutaneous T-cell pseudolymphoma has been reported with HIV infection in human patients.[7] All the cats that were tested for FeLV and FIV were negative. However, in a previous study, integrated FeLV provirus was identified in DNA tumour cells by PCR in one cat with epitheliotropic T-cell lymphoma that had negative serology.[14] Therefore, we cannot rule out the presence of FeLV provirus in lesional T-cells.

Apparently, systemic glucocorticoid therapy can provide clinical improvement in some cats (Table 1). Continuous administrations of glucocorticoids were required to maintain improvement. Some cats required more potent immunosuppressive therapy to control skin lesions or clinical signs of systemic disease. Prednisolone given in conjunction with chlorambucil or lomustine provided good to complete response in some cats. Although cats are known to be tolerant to glucocorticoid therapy, associated side effects can occur.[15] One cat in this study developed diabetes mellitus after receiving a single injection of methylprednisolone acetate and was euthanized (Table 3). Cyclosporine was reported to be occasionally effective in pseudolymphoma in humans.[5] However, development of cutaneous T-cell lymphoma has been reported in association with administration of cyclosporin in humans with atopic dermatitis and psoriasis.[16–18] For this reason, and because it is not known if some of the cases of feline cutaneous lymphocytosis in this study represent preneoplastic or neoplastic lesions, it may be prudent

not to use this medication. Doxycycline and tetracycline are other safe medications that were shown to be beneficial occasionally in pseudolymphoma in humans,[5] but have not been used for this purpose in cats. Surgery may be indicated in some cases of feline cutaneous lymphocytosis with solitary lesions.

In summary, cutaneous lymphocytosis appears to be a slow and relatively benign disease with a prolonged clinical course. Although some cats may decline and develop internal infiltration, the prognosis is not uniformly guarded. Underlying causes such as drug exposure or vaccination should be considered. It is important that pathologists do not hasten to a diagnosis of malignant lymphoma in these cases, thereby leading to premature euthanasia.

Unfortunately, histological and immunohistochemical evaluations did not predict the clinical outcome in cats with cutaneous lymphocytosis in this study. Although the development of systemic signs seems to be correlated with internal involvement, there is no single reliable criterion to differentiate cutaneous lymphocytosis from cutaneous lymphoma, and differentiation must be based on a combination of clinical, histological and immunohistochemical data, coupled with long-term outcome. Further studies, including analysis of T-cell receptor and immunoglobulin-H gene rearrangements and immunohistochemistry to further characterize lesional T-cell populations, are required and may provide predictive data by indication of clonal populations.

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Résumé 23 cas de lymphocytose cutanée, une maladie peu fréquente ressemblant histologiquement à un lymphome malin bien différencié, ont été étudiés sur le plan clinique, morphologique et immunohistochimique. Le pronostic était corrélé avec l'histomorphologie et l'immunotype. La maladie atteint surtout des chats âgés. Les lésions sont uniques dans 61% des cas et consistent en une alopécie (73.9%), de l'érythème, des squames et des ulcérations. La zone la plus fréquemment atteinte est la face latérale du thorax (43.5%). Un prurit est fréquemment

associé (65.2%). Des signes systémiques (anorexie et perte de poids) sont notés. Sur un plan morphologique, les lésions sont caractérisées par une infiltration dermique de lymphocytes T CD3+ (100%) bien différenciés et d'aggrégats de lymphocytes B CD79+ (64.3%). La lymphocytose cutanée évolue lentement et est relativement bénigne, bien que dans certains cas les signes systémiques conduisent à l'euthanasie. Quatre chats parmi les 12 animaux euthanasiés et un autre chat présentaient également des infiltrations lymphoïdes dans d'autres organes. Malheureusement, l'aspect histologique et immunologique des lésions cutanées ne permet pas de prédire l'évolution clinique de la maladie.

Resumen Se evaluaron las características clínicas, morfológicas e inmunohistoquímicas de 23 gatos con linfomatosis cutánea, una enfermedad infrecuente parecida histológicamente al linfoma maligno bien diferenciado. La evolución clínica fue correlacionada con las características histomorfológicas e inmunofenotípicas en un intento de predecir comportamiento benigno frente a maligno. La enfermedad afectaba principalmente gatos de edad avanzada. Las lesiones fueron solitarias en un 61% de los gatos y a menudo se caracterizaban por alopecia (73.9%), así como eritema, descamación y ulceración. El tórax lateral se encontraba afectado con mayor frecuencia (43.5%). El prurito era frecuente (65.2%). Los síntomas sistémicos incluían anorexia y pérdida de peso. Morfológicamente, las lesiones se caracterizaban por infiltraciones dérmicas de células T CD3+ bien diferenciadas (100%) y agregados de células B CD79+ (64.3%). La linfomatosis cutánea progresa de forma lenta y es relativamente benigna, aunque en algunos gatos los síntomas sistémicos llevaron a la eutanasia. Cuatro de los 12 gatos eutanasiados y un gato vivo mostraba también infiltrados linfoides en órganos internos. Desafortunadamente, la evaluación histológica e inmunohistoquímica de las lesiones cutáneas no podían predecir la evolución clínica.

Zusammenfassung Bei 23 Katzen mit kutaner Lymphozytose, einer ungewöhnlichen Krankheit, die histologisch dem gut differenzierten malignen Lymphom ähnelt, wurden klinische, morphologische und immunhistochemische Merkmale beschrieben. In dem Versuch, benignes versus malignes Verhalten vorauszusagen, wurde der klinische Verlauf mit Histomorphologie und Immunphänotyp in Korrelation gesetzt. Die Erkrankung befiel vorrangig ältere Katzen. 61% der Katzen zeigten Einzelläsionen, die sowohl durch Alopezie (73,9%) als auch Erythem, Schuppen und Ulzerationen charakterisiert waren. Der laterale Thorax war am häufigsten betroffen (43,5%). Oft war Pruritus vorhanden (65,2%). Zu den systemischen Anzeichen gehörten Anorexie und Gewichtsverlust. Morphologisch waren die Läsionen durch Infiltrationen mit gut differenzierten CD3+ T-Zellen (100%) und Aggregaten von CD79+ B-Zellen (64,3%) gekennzeichnet. Kutane Lymphozytose ist langsam progressiv und relativ benigne, obwohl bei einigen Katzen systemische Anzeichen zur Euthanasie führten. 4 von 12 euthanasierten Katzen und eine lebende Katze hatten lymphoide Infiltrationen in inneren Organen. Unglücklicherweise waren histologische und immunhistochemische Bewertungen der Hautläsionen nicht geeignet, das klinische Schicksal vorauszusagen.